Allergy Abstracts

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Volume 20, Number 5 September, 1955

Asthma and Hay Fever

Vaginal and Urinary Symptoms Following Pollen Injections: Report of a Case. Fox, J. L.: Ann. Allergy **13**: 187, 1955.

A 35-year-old woman with a history of grass pollinosis and urticaria was treated with house dust and grass extracts. During her first year of treatment the maximum dosage attained was 100 P.N.U. After having tolerated this dosage at weekly intervals for some time, the patient experienced severe pruritus vulvae following each of two similar weekly treatments. The hay fever responded favorably. The following season treatment was started at a very low level and was increased cautiously. When 30 P.N.U. were given, the patient again experienced severe pruritus vulvae and urticaria. Until the

pollen dosage was adjusted down to 0.4 P.N.U., the patient continued to experience the pruritic reactions. This low dosage at weekly intervals was tolerated without further difficulty and provided excellent relief from the hay fever. F.

Antihistamines by Injection in Allergic Desensitization. Malloy, C. J.: Canad. M. A. J. **72**: 375, 1955.

Twenty-four patients receiving hyposensitization therapy with pollens were given antihistamines parenterally, either combined with the extract or in an area near the injection site. Ten patients received 10 mg. of Histadyl in close proximity to the injection site. The other fourteen patients were given from 1 to 4 mg. of Chlor-tripolon in combination with the antigen in the same syringe. By combining the antigen with the antihistamine, it was possible to increase substantially the dose of pollen extract beyond the previous maximum level without constitutional or local reactions. Many of the patients (about 40 per cent) complained of mild side reactions, but it was unnecessary to discontinue treatment in any patients because of these reactions. Twenty-one of the patients obtained excellent results from their pollen therapy. The author suggests that it may be advantageous to give the antihistamine separately in an area close to the injection site rather than combined with the antigen, since both the dose of the extract and the antihistamine can then be measured more accurately. R. W.

Unexpected Death in Asthma. Maxwell, J.: Dis. Chest **27**: 208, 1955.

Unexpected death was reported in nine patients with bronchial asthma whose ages varied from 42 to 67 years. The total duration of the illness in these patients varied from five months to ten years; in each, the asthma had started after the age of 30 years. The family history was positive for asthma in two cases. Positive skin reactions were reported in one patient. Five of the patients had associated upper respiratory disease. Bronchopulmonary changes were noted in only one case. It was thought that psychological factors were important in all nine cases. One patient had hypertension and one had an enlarged heart. In each of the patients, death occurred in the middle of what was regarded as an ordinary attack of asthma. Each of the nine patients exhibited a defeatist attitude almost from the beginning of his illness, and seven had expressed a conviction of impending death. It was concluded that patients whose asthma begins after the age of 45 and those who exhibit a depressive tendency are more liable to this disaster. E. W.

Dermatology

Studies on Fungi Encountered in the Atmosphere. II. Production of Dermatitis in Guinea Pigs by Crude Ether-Soluble Extracts of Alternaria, Hormodendrum, Penicillium and Aspergillus. Bocobo, F. C., Curtis, A. C., Block, W. D., and Stubbart, F. J.: J. Invest. Dermat. **23**: 489, 1954.

Crude oily ether extracts were made from cultures of alternaria, hormodendrum, penicillium, and *Aspergillus niger*. The extracts were painted daily on epilated skin sites of guinea pigs for from 2 to 4 weeks. Plain ether and ether extracts of the agar medium served as controls. A majority of animals painted with extracts of alternaria, penicillium, or aspergillus developed an eczematoid dermatitis at the primary site of application. None of the animals painted with hormodendrum extract or with the control substances developed

skin lesions. All animals were tested by the application of each extract on distant sites. Testing was carried out on the tenth day of painting, again at the height of the primary dermatitic reaction, and four weeks later when painting had been stopped and the lesions were subsiding. The development of an erythema after twenty-four to forty-eight hours was considered a positive reaction. No positive reactions occurred on testing with hormodendrum, penicillium, or aspergillus extracts. Five of the eight animals originally treated with alternaria extract developed positive reactions to alternaria extract. One reaction was doubtful (±) and the others ranged between two-plus (++) and three-plus (+++). Positive skin reactions could be evoked after daily painting had been stopped and the primary lesion had healed. The five animals which showed positive reactions had developed dermatitis at the primary site. The remaining three alternaria-treated animals who were skin test negative had failed to develop a primary dermatitis. The alternaria extract failed to produce positive reactions in any animals of the other groups. Control animals were negative to all extracts. Microscopic examination of biopsy specimens taken from typical primary lesions in each group of animals demonstrated findings consistent with an eczematoid dermatitis. The results of this study indicate that ether extracts of alternaria, penicillium and aspergillus contain a substance capable of inducing eczematoid dermatitis in guinea pigs. This was not true of extracts of hormodendrum. The penicillium and aspergillus extracts appeared to act as primary irritants, while the alternaria extract seemed to possess the properties of a contact sensitizer.

M. C.

Treatment of Rhus Dermatitis With Topical Hydrocortisone. A Clinical Evaluation. Eskind, I. B., Sigafoos, R. B., and Kelso, R. W., Jr.: Arch. Dermat. & Syph. **69**: 410, 1954.

Hydrocortisone was prepared in four different concentrations for topical use in the treatment of Rhus dermatitis. The hormone was incorporated into various vehicles and used for therapy in the following preparations: 0.2 per cent lotion; 1 per cent ointment; 2.5 per cent ointment; and 2.5 per cent cream. Seventy-seven patients suffering from acute Rhus dermatitis were treated with the various preparations; fifteen patients similarly afflicted were given placebo therapy. The physician following the patients' clinical course had no knowledge as to which medication each patient received. The percentage of improvement observed was essentially the same in the treated and in the control groups. The time of institution of therapy and the severity of the dermatitis were not factors in determining the degree of beneficial results obtained. In four patients in whom symptoms were manifested primarily by severe angioedema, rather than by pruritus, redness, and vesiculation, topical hydrocortisone produced dramatic results within 6 to 24 hours. The authors conclude that, for the typical case of Rhus dermatitis, topical hydrocortisone is of no benefit, but that, in special cases manifesting severe angioedema, it may be a most effective form of therapy.

R. W.

Recovery of Normal and Eczematous Skin From Alkali. Control of Surface pH By Exchange Resins. Cornbleet, T., and Joseph, N. R.: J. Invest. Dermat. **23**: 455, 1954.

The pH of the skin of the dorsal surface of the hands of normal persons and of those with atopic eczema was measured by a potentiometer. Each hand was then immersed in an alkaline soap mixture for 10 minutes and

wiped with a towel. The pH was again measured at intervals of one minute and a curve of pH recovery was determined. Similar experiments were carried out using dilute NaOH solutions. The pH of normal skin was found to be more acid than that of eczematous skin. After soaping, both types of skin reached about the same slightly alkaline pH. However, recovery after soaping was more rapid in the normal group. After 20 minutes, the normal skin was almost halfway to full recovery, whereas the eczematous skin showed little evidence of recovery and was still in the alkaline pH range.

The effect of a cation exchange resin on the pH recovery of skin tested with soap or with alkali was also determined. In normal persons, the application of a hydrogen ion-donating resin before soaping lessened the alkaline influence of the latter, but delayed pH recovery. Application of the resin after soaping hastened the recovery considerably. Similar findings occurred with eczematous skin, but the fluctuations in pH induced by soap and resin were greater than those observed in normal persons. It was suggested that the eczematous skin has less defense against the effects of soap since it does not neutralize alkali as rapidly as does the skin of normal persons.

M. C.

Studies on Fungi Encountered in the Atmosphere. I. The Presence of Fungous Spores and of Pollens in KOH Preparations. Bocobo, F. C., and Curtis, A. C.: J. Invest. Dermat. **23**: 479, 1954.

In studying routine KOH mounts of skin scrapings obtained from patients in a large clinic in Michigan, the presence of fungous spores was noted. Spore counts were made on these preparations according to the method employed in counting pollen granules. Except for a very occasional helminthosporium spore and a rare cluster of hormodendrum spores, alternaria spores were almost the only ones encountered. The frequency with which alternaria spores were found in the KOH mounts roughly paralleled the incidence of these spores in the atmosphere. Peak concentrations of molds were present in the air and in the KOH mounts from July through September. No spores were found in the KOH mounts during the winter months, a period when the atmosphere is devoid of spores. Air-borne pollens of all varieties, especially ragweed pollen, were also found in these preparations. Pollens were encountered more frequently and in greater numbers than spores.

M. C.

Contact Dermatitis From Chlorcyclizine Hydrochloride (Perazil) Cream. Report of Four Cases. Ayres, S., III, and Ayres, S., Jr.: Arch. Dermat. & Syph. **69**: 502, 1954.

Four cases of contact sensitivity to 1 per cent Perazil cream were observed. Three of the patients had used the cream topically before developing the sensitivity, while the fourth had been using Pyribenzamine ointment locally, but had taken Perazil by mouth just prior to the exacerbation of the eruption. This patient also had a positive patch reaction to the Pyribenzamine ointment. In one patient, two years had elapsed between the initial exposure to Perazil ointment and the exposure which resulted in contact dermatitis. All of the cases showed positive patch responses to the Perazil cream and negative reactions to the ointment base. Among several hundred patients treated topically with 1 per cent Perazil ointment, the authors encountered only four cases of specific sensitivity. They conclude, therefore, that Perazil ointment is a poor sensitizer and is reasonably safe for topical therapy.

R. W.

Dermatitis of the Feet Due to Shoes. Shatin, H., and Reisch, M.: Arch. Dermat. & Syph. **69**: 651, 1954.

Severe pedal contact dermatitis from shoes was studied in 31 patients who had required hospitalization because of this complaint. Most of the reactions occurred on the dorsal surface of the toes and were manifested by erythema, scaling, and vesiculation. In many patients the eruption spread to involve the distal half of the foot and occasionally even involved the interdigital webs or the plantar surface. A few patients also developed similar rashes on their heels, while one had an eruption limited to the soles of his feet. The dermatitis usually produced severe pruritus and was often confused with dermatophytosis. Patch tests were made with the following materials used in the manufacture of shoes: leather, waterproofed paper, flannel box toe, thermoplastic box toe, cotton drill lining, midsole (ground cork-rubber mixture), reclaimed rubber, and rubber asphalt filler. It was found that the thermoplastic toe and the various rubber products were the major excitants of the contact sensitivity. Since the thermoplastic toe contained various forms of scrap rubber, it appeared that rubber was the actual cause of the dermatitis. There was only a relative correlation, however, between the positive reactions obtained with the thermoplastic toe and the various forms of rubber. The actual excitants in rubber sensitivity are the accelerators and antioxidants in rubber and not rubber itself. Many different types and combinations of accelerators and antioxidants are used in the manufacture of rubber and the authors state that this fact may possibly explain some of the discrepancies in patch reactions observed in their patients. When the heel area, rather than the toe area, was affected, the rubber cement used to glue the heel pad to the sole was usually found to be the causative factor. When patients changed from shoes with thermoplastic toes to more expensive shoes which contained a flannel box toe, the dermatitis subsided quickly. The authors stress the importance of rubber compounds, especially those used in making the thermoplastic box toe, as a cause of contact eczematoid dermatitis of the feet.

R. W.

The Effect of X-rays on Experimentally Produced Acute Contact Dermatitis. Kemp, T. S., and Kligman, A. M.: J. Invest. Dermat. **23**: 423, 1954.

Nine human subjects were experimentally sensitized to 2:4 dinitrochlorobenzene by standard techniques. Rectangular patches of moderately intense dermatitis measuring 2 by 7 cm. were then produced on the back of each sensitized subject by application of the antigen. Radiation was delivered to one-half of the rectangular area of dermatitic skin, the other half being left unexposed for control observations. X-ray therapy was applied either as a single dose or over a three-day period, beginning immediately after the eliciting application of the antigen or at the peak of the cutaneous reaction. In all the areas of dermatitis so treated, the results were uniformly negative. In one instance, there was a slight interference in the development of the inflammatory reaction when fractionated radiation had been given at the time of application of the eliciting dose of antigen. There was no evidence of accelerated healing on any patch treated at the height of the allergic reaction. These experimental findings indicate that x-ray therapy is of doubtful value in the treatment of acute allergic contact dermatitis.

M. C.

A Therapeutic Assay of Topically Applied 9 α-Fluorhydrocortisone Acetate in Selected Dermatoses. Witten, V. H., Sulzberger, M. G., Zimmerman, E. H., and Shapiro, A. J.: J. Invest. Dermat. **24**: 1, 1955.

The therapeutic effectiveness of topical preparations containing 9 α-fluorhydrocortisone acetate was compared with that of preparations containing hydrocortisone-free alcohol of the same concentration. Each preparation was applied simultaneously to one of two symmetrically situated dermatitic areas in 51 patients with various dermatoses. Fluorhydrocortisone was more effective than the hydrocortisone in 28 cases, equally effective in 16 cases, and less effective in 5 cases. In 2 cases, both medications were equally ineffective. In the 28 cases of atopic dermatitis in this series, fluorhydrocortisone-treated areas showed greater improvement than the hydrocortisone-treated lesions in 5 cases, slightly greater improvement in 10 cases, equal improvement in 11 cases, and less improvement in 2 cases. In 7 cases of allergic contact dermatitis, the fluorhydrocortisone was more effective than the hydrocortisone in 2 cases, slightly more effective in 2 cases, equally effective in 1 case, and less effective in 1 case. These findings indicate that 9 α-fluorhydrocortisone acetate was slightly more efficacious than hydrocortisone-free alcohol in the topical treatment of the dermatoses selected for this study. M. C.

Prednisone in Treatment of Selected Dermatoses. Preliminary Report. Robinson, H. M., Jr.: J. A. M. A. **158**: 473, 1955.

Eleven patients with dermatoses were treated with the new synthetic steroid, prednisone. During the period of treatment all local applications and other systemic therapy was withheld. There were four patients with atopic dermatitis. One was a 3-year-old child who received an initial total daily dose of 30 mg. of prednisone. Within five days, marked improvement was noted and, in fourteen days, the lesions had completely disappeared. The dose of prednisone was reduced by 2.5 mg. every four days until a maintenance dose of 7.5 mg. was established. The remaining patients with atopic dermatitis were adults and were started initially on 60 mg. of prednisone daily in divided doses. All improved within seven days with complete involution of lesions in from fourteen to twenty-one days. The dose of prednisone was reduced by 5 mg. every four or five days to reach a maintenance dose of 15 mg. daily in two patients and a dose of 20 mg. daily in the other. When the dose was reduced below these levels, symptoms recurred. Equally effective clinical results were obtained in two cases of pemphigus vulgaris, two cases of acute disseminated lupus erythematosis, and three cases of exfoliative dermatitis.

Prednisone was found to be from four to five times as active in these conditions as cortisone, hydrocortisone, or corticotropin without producing more frequent or severe undesirable side effects. Laboratory studies in this series of patients revealed no disturbance in electrolyte balance. A significant decrease in circulating eosinophils occurred following the administration of the drug. M. C.

An Evaluation of Hydrocortisone Acetate Ointment in Various Skin Diseases. Kalz, F., McCorriston, L. R., and Prichard, H.: Canad. M. A. J. **72**: 7, 1955.

Five hundred eighty-one patients suffering from a variety of skin diseases were treated with hydrocortisone acetate ointment. The hydrocortisone acetate was incorporated into various ointment bases in concentrations ranging from 1 to 2.5 per cent. There were 75 patients with atopic dermatitis, 49 with contact

dermatitis, and 131 youngsters with infantile eczema. Among the infantile eczema group, the authors included almost all types of rashes seen in infancy, such as atopic dermatitis, seborrheic dermatitis, primary irritant eruptions, contact dermatitis, and a large group of cases where a definitive diagnosis could not be established. The patients were advised to apply the ointment twice daily. About 66 per cent of the patients with atopic dermatitis obtained moderate relief, while 25 per cent had excellent results. The hydrocortisone ointment appeared to be superior to the tar pastes, as was clearly demonstrated in those cases where paired ointments were used as controls. Individuals with contact dermatitis obtained almost 100 per cent relief with hydrocortisone, and about 90 per cent were either cured or had a complete remission. The vast majority of cases classified under infantile eczema improved very considerably. Cure or complete control occurred in cases of contact dermatitis or primary irritation. It was noted that, in some cases, it was necessary to increase the concentration of hydrocortisone in order to maintain the clinical improvement. Apparently, the hormone tends to lose its effect after prolonged use.

A water-in-oil emulsion appeared superior to all other types of vehicles employed. No evidence of systemic effects from absorption of the hydrocortisone was observed. Local reactions to the various types of hydrocortisone preparations were encountered in 12 individuals. In all cases, the ointment base rather than the hormone was found to be the etiological factor. Carbowax was usually the offending agent because of its drying properties or because of the development of allergic sensitization to it. In a few cases, petrolatum and oily cold creams were not well tolerated. Secondary infection in the treated area developed in 4 patients; in such cases, the authors suggest the advisability of incorporating an antibiotic of low sensitizing properties into the hydrocortisone ointment. Infections were most frequently encountered in rashes in the perigenital, perianal, or axillary region. The authors conclude that hydrocortisone is a most effective agent in the treatment of acutely inflammatory pruritic skin conditions. R. W.

Otorhinology and Ophthalmology

Vernal Conjunctivitis. Alimuddin, M.: Brit. J. Ophth. **39**: 160, 1955.

A clinical study was made of a series of 1,871 cases of vernal conjunctivitis seen during a three-year period in West Pakistan. Approximately one-third of all ophthalmological cases seen during the summer months were affected by this condition. About 59 per cent of the patients afflicted were between the ages of 10 and 20 years. Three times as many males were affected as females. Three clinical types of the disease—the palpebral, limbal, and an irritative type—were found to be evenly distributed among the group. The irritative type of vernal conjunctivitis had not been previously described. In this type, the eyes had a slightly congested appearance, the pericorneal area being involved, while the palpebral and ocular conjunctiva remained clear. Slit-lamp examination revealed vessel engorgement of the pericorneal vessels, including the deep ciliary plexus and an increase in the number of aqueous veins. Hypertrophy, vegetation, ropy discharge, and milky appearance were frequently lacking in this type of vernal conjunctivitis. Conjunctival scrapings always showed from 3 to 5 eosinophils per field. The most commonly associated allergic conditions were eczema, urticaria, angioneurotic edema, and contact dermatitis. Occasionally intestinal parasitic infestations were found. About 30 per cent of the cases with the irritative type of conjunctivitis converted to the limbal type within the three-year period, while none developed into the palpebral type. B. S.

Miscellaneous Allergies

The Use of Procaine Amide in the Treatment and Prevention of Penicillin Reactions. Jennings, P. B., and Olansky, S.: Ann. Int. Med. **40**: 711, 1954.

The effect of procaine amide (Pronestyl) in the treatment of penicillin reactions was studied. Twenty-four patients with allergic reactions to penicillin were treated with Pronestyl. These patients each had received from 400,000 to 12,000,000 units of penicillin; the reactions had occurred within 5 to 39 days following the initial dose. The average dose of Pronestyl given was 250 mg. every six hours, and the total dosage varied from 1 to 14 Gm. Factors considered in the clinical response were: speed of response, disappearance of symptoms and signs, length of hospitalization, and occurrence of relapses. Twenty-two of the twenty-four patients had excellent or good results, while two showed fair responses to the drug.

Seventeen patients with penicillin reactions served as controls and were treated with Benadryl. The penicillin dosage in this group varied from 300,000 to 6,000,000 units, and the reactions had appeared from 2 to 16 days after the initial dose. The dose of Benadryl was 50 mg. every six hours; the total dosage varied from 0.6 to 2.8 Gm. Eleven patients showed excellent or good results, three showed fair responses, and three responded poorly.

It was concluded that Pronestyl was at least as effective as Benadryl in the treatment of penicillin reactions, and possibly somewhat better. The drug is relatively nontoxic and no significant untoward effects were noted.

Procaine amide was used prophylactically to prevent reactions in patients with definite histories of previous allergic reactions to penicillin. Despite the history of penicillin sensitivity, penicillin was administered to these patients whenever it was indicated. The dosage in this group varied from 900,000 to 9,000,000 units of penicillin. Pronestyl was given concomitantly, usually 250 mg. every six hours throughout the course of penicillin, and generally for seven days after penicillin was discontinued. The total dosage of Pronestyl given varied from 3 to 45 Gm. Only 4 of 18 patients so treated developed allergic reactions; in 3 of the 4 the symptoms developed after the Pronestyl had been discontinued. Pronestyl was regarded as being useful in the prevention of such allergic reactions. Skin testing with penicillin was not reported.

J. S.

Anaphylactogenic Properties of Piperazine Citrate. Ratner, B., and Flynn, J. G.: Ann. Allergy **13**: 176, 1955.

Piperazine citrate (Antepar), which is used extensively in the treatment of *Oxyuris vermicularis* and *Ascaris lumbricoides* infestations, has been reported as a cause of a number of dermal allergic reactions.

In an attempt to evaluate the anaphylactogenic properties of piperazine, a series of guinea pigs was given 4 intraperitoneal or subcutaneous injections of a fixed amount of the medication over a period of 9 days. Twenty-one days later, a challenging dose of the material was administered intravenously. No evidence of sensitivity was elicited. A second series of 37 guinea pigs was given 6 daily preparatory intracutaneous injections of the syrup. After one week, a second series of intracutaneous injections was given. Sixteen days following the last preparatory injections, the animals were given an intravenous injection of the drug without untoward effects. Another series of guinea pigs, prepared in a similar fashion, was challenged with an intracutaneous dose. No immediate or

delayed reactions were noted. When the material was combined with Freund's adjuvant and injected into a third series of animals, no evidence of sensitivity could be elicited after 20 days by an intracutaneous dose or after 22 days by the intravenous route.

On the basis of these findings, it is concluded that piperazine possesses no allergenic properties. F.

Analysis of Proteins of Bovine Lens, Vitreous, and Aqueous by Electrophoresis and by Oudin's Gel Diffusion Technique. Rao, S. S., Kulkarni, M. E., Cooper, S. N., and Radhakrishnan, M. R.: Brit. J. Ophth. **39**: 163, 1955.

The electrophoretic pattern of dialysed solutions of normal bovine serum, whole lens, alpha-crystallin, whole lens minus alpha-crystallin, aqueous, and vitreous, were determined. The pattern obtained with the serum resembled that of any mammalian serum. The whole lens solution showed three peaks, corresponding to alpha-, beta-, and gamma-crystallin, with the alpha fraction being the fastest moving component. The electrophoretic pattern of aqueous humour resembled that of whole lens. The peaks obtained with vitreous humour were similar to those of serum, with the exception that vitreous contained larger amounts of gamma-globulin.

The protein content of the aforementioned solutions was further analyzed by Oudin's gel diffusion technique. The antigen solutions were layered on agar containing rabbit antilens, antivitreous, and antiaqueous sera. The number of bands which formed at the junction of the two layers indicated the minimum number of antigens in each preparation. The size of the band was regarded as a measure of the concentration of the antigen. These studies indicated that bovine lens contained large amounts of alpha-, beta-, and gamma-crystallins and small amounts of the other three proteins. These proteins were not antigenically related to bovine serum protein. Six proteins were found in aqueous humour, three in common with lens proteins and three in common with serum proteins. Vitreous humour contained at least seven proteins, five in common with serum proteins and at least two in common with lens proteins.

Since lens and blood proteins differ antigenically, it is possible to develop sensitization to one's own lens protein, resulting in the pathologic condition of endophthalmitis phacoanaphylactica. The presence of lens proteins in aqueous and vitreous suggests that any injury to these humours may cause their proteins to enter the blood stream and induce sensitivity to lens protein. It is suggested that lens proteins are excreted into the aqueous through the lens capsule and are destroyed by proteolytic enzymes there. If they were not so destroyed, anaphylaxis from this source would be very common. B. S.

Löffler's Reaction to Para-aminosalicylic Acid. Tuchman, H.: Am. Rev. Tubere. **70**: 171, 1954.

Several months after the institution of therapy with PAS and streptomycin, a 21-year-old white male with minimal tuberculosis of the left lung developed fever, cough, headache, anorexia, and a blood eosinophilia of 26 per cent. Roentgenograms suggested that the infiltrative process was spreading to the other lung or that acute bilateral pneumonitis was developing. Withholding the PAS resulted in clearing of the lung fields roentgenographically and the disappearance of the eosinophilia. Reinstitution of treatment with a different form of the medication (calcium PAS in tablet form) was followed by a recurrence of the allergic phenomenon which was interpreted as a Löffler type reaction to PAS therapy. E. W.

Swelling of the Interphalangeal Joints as a Manifestation of Drug Allergy. Spring, M.: Ann. Allergy **13**: 160, 1955.

Three cases are reported in which sensitivity to drugs was manifested by swelling of the phalanges of the hands. Sulfathiazole, penicillin, and desiccated thyroid were the suspected sensitizing agents. In the cases in which sulfathiazole and penicillin were the suspected offenders, no corroborative evidence could be obtained. In the patient in whom thyroid appeared to be the sensitizing drug, the clinical picture was reproduced on two occasions by reinstitution of thyroid therapy. F.

Anaphylaxis

Toxicity of Histamine and Antagonism Between Histamine and Antihistamines in Various Strains of Mice. Ambrus, J. L., Guth, P. S., Goldstein, S., Goldberg, M. E., and Harrisson, J. W. E.: Proc. Soc. Exper. Biol. & Med. **88**: 457, 1955.

The toxicity of histamine was compared in four strains of mice. The older and heavier mice within a single strain were found to be more resistant to histamine than younger and lighter ones. The degree of protection observed by pretreatment with an antihistamine was then compared in the various strains. Those strains which were most histamine resistant and the older and heavier mice within a strain were least protected by the antihistamine. These findings probably explain the discrepancies in the results of similar previously reported studies. The authors suggest that histamine toxicity may be manifested through two different mechanisms. The antihistamines antagonize the mechanism most operative in the histamine-sensitive animals. The mechanism operative in histamine-resistant animals is not antagonized by the antihistamines. B. S.

Pharmacology, Physiology, and Pathology

The Question of Reactions to Mercurial Diuretics. Brown, E. A.: Ann. Allergy **13**: 131, 1955.

Serious reactions to the mercurial diuretics have become less frequent since the introduction of currently used medications. Many of the untoward reactions to these drugs can be ascribed to the patient's physiologic response to the induced diuresis rather than to a sensitivity mechanism. Diuresis may result in sodium, calcium, and potassium deficiency, in hemoconcentration, digitalis toxicity, vitamin deficiencies, and attacks of gout. These reactions can be avoided by judicious use of the drugs from the standpoint of dosage, rate of administration, and careful handling of the patient. The mercurial diuretics usually act as intact organic complexes rather than as free mercury and, as such, rarely, if ever, cause mercurialism. Overdosage, however, may produce signs of toxicity. Gingivitis, stomatitis, and gastrointestinal symptoms are not uncommonly seen in patients under treatment. They can be easily controlled by proper dosage and patient care.

Skin reactions to the mercurials include generalized pruritus, urticaria, morbilliform or purpuric eruptions, and very rarely, exfoliative dermatitis. They usually occur alone, but may be accompanied or followed by chills, fever, and asthma. These reactions apparently are of an allergic nature. When they occur they should be recognized as a warning of the possibility of more serious reactions to subsequent administration of the drugs. Certain patients are sensitive to the organic compound and not to the mercury. Others are sensi-

tive to the mercury in one of the conjugates but not to the mercury in a slightly different conjugate. Such patients may react to one mercurial diuretic and not to another; however, cross sensitivity to the various mercurials does exist. Intradermal and patch tests are not reliable, but the reverse passive transfer technique may demonstrate an existing sensitivity. Sensitivity is often of a temporary nature. Although the presence of albuminuria is, of itself, not a contraindication to the use of the mercurials, extreme caution should be exercised in the administration of mercurial therapy to patients with acute glomerulonephritis or chronic renal disease. F.

A New Antihistamine for Treatment of Various Allergic Manifestations. Clein, N. W.: Ann. Allergy **13**: 163, 1955.

Sandostene (1-methyl-4-amino-N′-phenyl-N′-(2′-thenyl)-piperidine tartrate), a new antihistamine, was used in the treatment of a series of 124 allergic children suffering from hay fever, eczema, pollen asthma, perennial allergic rhinitis, urticaria, and angioneurotic edema. The drug was used alone in the form of 25 mg. tablets and in combination with calcium for intravenous administration and as a syrup for oral administration. The calcium was combined with the antihistaminic because it is believed that this combination enhances the effect of the antihistaminic by decreasing tissue permeability. Good or excellent results were obtained in 32 of the 76 hay fever cases and in 9 of 12 cases on whom a diagnosis of pollen asthma and hay fever had been made. The younger children were given the syrup and the older children received the tablets. Five of seven patients of angioneurotic edema and urticaria who were given intravenous injections experienced excellent results. In the entire series there were only two instances of toxic manifestations from the medication, and both of these were of minor significance. No drowsiness was noted. F.

A Quantitative Method for the Determination of Antihistaminic Compounds Containing the Pyridine Radical. Perlman, E.: J. Pharmacol. & Exper. Therap. **95**: 465, 1949.

The cyanogen bromide test for pyridine was applied to antihistamine drugs containing this radical. A blue fluorescence in filtered ultraviolet light resulted instead of the usual color reaction. The technique is described in detail, as is the relationship of color or fluorescence to chemical structure. Studies of urine from patients who were given Pyribenzamine or Thenylene, orally or intravenously, revealed that with either method of administration the maximum rate of excretion occurs in between one and one-half and four and one-half hours. A significant amount is excreted in from eight to ten hours. About 6 to 10 per cent of the amount of ingested drug appears in the urine. It appears that virtually all the drug is absorbed from the gastrointestinal tract and is rapidly removed from the blood stream. The antihistamine excretion product is firmly combined with a small acidic radical. Heating with alkali liberates an active antihistaminic which, on combination with picrate, has the same melting point as Pyribenzamine picrate. K.

Studies on the Mechanism of the Shwartzman Phenomenon. Similarities Between Reactions to Endotoxins and Certain Reactions of Bacterial Allergy. Stetson, C. A., Jr.: J. Exper. Med. **101**: 421, 1955.

Tuberculin reactions in BCG-sensitized rabbits were found to be comparable in several respects to Shwartzman reactions to endotoxins from gram-

negative bacilli. In both cases a similar delayed inflammatory response could be elicited which was, roughly, proportional to the dose of material injected. Repetition of these injections in the same area induced hemorrhagic necrosis in both cases when sufficiently large doses were used. Epinephrine injected into the skin of the reacting site intensified both types of skin lesions. The intracorneal injection of meningococcal toxin, used as a test for cellular hypersensitivity as opposed to vascular reaction, produced clouding followed by pannus formation. Similar results were obtained with 10 μg. doses of purified somatic antigen of *Shigella paradysenteriae*. The fever curves resulting from the intravenous injection of endotoxin were very similar to those from tuberculin in sensitized rabbits. Rabbits not sensitized with BCG failed to show febrile responses to tuberculin. Leukopenic reactions after intravenous injection were noted after either endotoxin or tuberculin, the latter in sensitized rabbits. Cutaneous vasoconstriction, "ear vascular reaction," was noted in both groups. Normal rabbits did not show this reaction to tuberculin. Rabbits were sensitized with a single intracutaneous injection of BCG vaccine. The intracutaneous injection of OT about three weeks later elicited typical delayed reactions. These reaction sites were further activated by the intravenous injection of meningococcal endotoxin. Normal rabbits showed no cutaneous reaction to the initial cutaneous test with OT and the site so tested was not affected by intravenous meningococcal toxin. When meningococcal agar washings were injected intracutaneously in BCG-sensitized and control animals, the subsequent injection of tuberculin intravenously elicited typical Shwartzman reactions at the meningococcal sites in the sensitized rabbits but not in the control animals. Tuberculin could be substituted for meningococcal toxin in these sensitized rabbits with the same results. When heat-killed Group A streptococci in four dilutions were injected intracutaneously at the same time, small nodular lesions appeared. From ten to fourteen days later, the same doses were repeated and a more exaggerated response was obtained. The intravenous injection of meningococcal agar washings at the height of these local reactions produced typical Shwartzman hemorrhage and necrosis. Thus far, tuberculin intravenously has not been capable of eliciting a generalized Shwartzman reaction.

The consistency found throughout these comparisons seems to indicate that some basic mechanism may be common both to the Shwartzman reaction and to tuberculin-type bacterial hypersensitivity. K.

Miscellaneous

Major Undesirable Side-Effects Resulting From Prednisolone and Prednisone. Bollet, A. J., Black, R., and Bunim, J. J.: J. A. M. A. **158**: 459, 1955.

Serial gastroduodenal x-ray studies were done at six-week intervals on eighteen patients receiving treatment with prednisolone or prednisone. Peptic ulcers developed in three patients, an unusually high incidence of this complication in steroid-treated cases. There was no relationship between the appearance of the ulcer and the duration of therapy or the total dose of the drug administered. The ulcers produced no symptoms, which indicated that careful observation of patients receiving these drugs was essential in order to prevent sudden perforation or hemorrhage. The authors quote an unreported case of massive hematemesis which followed a course of prednisolone. Under the usual medical regimen for peptic ulcer, radiologic evidence of healing was noted within three weeks in each case. It was suggested that aluminum hydroxide gel be given routinely to patients receiving the newer steroids, in the hope of reducing the incidence of peptic ulcers. In one patient with a

psychoneurotic background, a severe depressive psychosis developed during therapy. This indicated that patients must be carefully selected for treatment with these newer steroids. M. C.

Immunologic Unresponsiveness Induced by Protein Antigens. Dixon, F. J., and Maurer, P. H.: J. Exper. Med. **101**: 245, 1955.

Large amounts of readily catabolized antigen in the form of human plasma or bovine serum albumin were administered daily for from 43 to 112 days to rabbits by the intravenous and subcutaneous routes. Some of the rabbits were injected from the time of birth, others were adult when injected, and still others were subjected to whole body x-radiation 2 days prior to their infusions of antigen. The rate of loss of foreign protein from the plasma of the recipients was followed quantitatively. Antibody formation was also measured.

The rate of disappearance of antigen from circulation under these conditions was similar to that for catabolism of autologous protein. Human serum albumin could be detected 81 days and gamma globulin 68 days after cessation of human serum injections in adult rabbits, for 75 days in newborn rabbits and for 102 days in irradiated rabbits. There was no evidence of antibody formation to the major antigen injected during the intensive antigen administration. Adult rabbits, within 4 to 6 months of their intensive treatment and after disappearance of all antigen from their circulation, recovered their ability to make an immune response. Of 2 groups of irradiated animals and 2 "newborn" groups, none of the animals regained this ability over a 7- to 9-month postinfusion observation period. All rabbits, however, showed immune responses to serum protein antigens other than those used in the infusions. All the rabbits made antibody responses to minor constituents of the infusions. Serum fractions I, II, III, and IV in the animals treated with human plasma elicited antibodies, whereas human serum albumin and gamma globulin did not. The bovine albumin used contained less than 0.01 per cent of bovine gamma globulin. Animals injected with heavy doses of this preparation showed antibody formation only to the gamma globulin. Passively administered rabbit antihuman albumin was injected into the unresponsive newborn rabbits treated with human plasma to see whether persistent circulating antigen was responsible for the failure to detect circulating antibody. This antihuman albumin disappeared from the circulation at a rate corresponding to that for homologous gamma globulin in contrast to the rapid disappearance of antibody when circulating antigen is present. Similar results were obtained with bovine albumin in animals unresponsive to this material despite its injection in heavy doses. The offspring of a female injected with bovine albumin from birth and permanently unresponsive to this material and of a male temporarily unresponsive to bovine albumin reacted with a primary type immune response to a small dose of bovine albumin at 1 month of age and showed an anamnestic response 3 months later. Severe serum sickness developed in the human-serum-treated animals within 1 to 2 weeks and lasted 4 to 5 weeks after the start of the infusion. Arteritis, myocarditis, and endocarditis were observed and, since no antibody could be detected for the albumin or globulin fractions, it is considered likely that other fractions were responsible. Anemia also occurred in these rabbits, with splenic enlargement and hyperplasia of bone marrow. The anemia reverted to normal after injections ceased and was less severe in newborn and irradiated animals. No serum sickness lesions developed in the bovine-albumin-treated animals, although it is known that a single injection of bovine albumin will produce this illness in from 60 to 89 per cent of rabbits. The massively treated animals showed no morphologic lesions which could account for their immunologic unresponsiveness.

K.

Shwartzman Phenomenon in Fatal Infantile Diarrhea Due to Escherichia Coli 0-111, B4. McKay, D. G., and Wahle, G. H., Jr.: Lancet **2**: 1199, 1954.

Several cases of infantile diarrhea which terminated fatally are discussed. Clinically, the disease was characterized by severe and protracted diarrhea, vomiting, fever, severe dehydration, acidosis, respiratory distress, vasomotor instability, paralytic ileus, focal hemorrhages, shock, and occasional convulsions. At post-mortem, the most constant macroscopic observations were dehydration, emaciation, skin petechiae, distention and dilation of the small bowel, diffuse congestion and edema of the gastrointestinal mucosa, and small areas of hemorrhage and ulceration in the small and large intestines. Microscopically, there was diffuse inflammation of the intestinal mucosa with a tendency toward excessive mucus production. There were many areas of superficial mucosal ulceration as well as small focal hemorrhages and necrotic lesions. The outstanding pathologic finding was intravascular fibrin thrombosis of capillaries and precapillary arterioles in the lungs, liver, brain, spleen, adrenals, and kidneys. "Perivascular infiltrations with polymorphs and macrophages as well as intravascular accumulations of these cells were most prominent in the brain, spleen, and lung. The amount of thrombosis varied but in the more severely affected kidneys, every glomerular tuft was completely occluded by a fibrin thrombus." The authors found the renal lesion to be identical with the reaction seen in rabbit kidneys following a generalized Shwartzman reaction. They postulate that, after the intestinal mucosa is damaged in infantile diarrhea, it permits the active Shwartzman material to be absorbed into the blood stream. They suggest that the active Shwartzman materials—whether from a specific microorganism, from bacteria of the intestinal flora, or from products of cellular intestinal necrosis—repeatedly gain access into the circulation and thus prepare and provoke the local and generalized Shwartzman phenomenon in these infants. R. W.

Reactivation of Non-Infective Virus in a Cortisone-Injected Host. Kilbourne, E. D.: J. Exper. Med. **101**: 437, 1955.

Influenza B virus, Lee strain, was partially inactivated by various thermal techniques. Low yields of viral hemagglutinin (1:16) were obtained in chick embryo eggs inoculated with this preparation, whereas active virus under the same conditions yielded somewhat higher titers (1:80). When the eggs were treated with cortisone, there was a striking increase in the concentrations of virus, regardless of whether the inoculum had been inactivated (1:768) or not (1:640). When inactive virus was added to active virus in the inocula the viral yield, as measured by hemagglutinin titers (1:48), was intermediate between that obtained with either preparation singly and not a summation of the effect of the increased dosage. When the same combination was administered to cortisone-treated eggs the final viral yield (1:768) was somewhat greater than when active virus alone was injected into cortisone-treated eggs. When viral preparations were diluted so as to reach an end point of infectivity and injected into eggs, there was no difference in titer when the indicator eggs were treated with cortisone. When noninfective Lee strain virus was injected into eggs, followed two hours later by fully infective virus of PR8 strain, the growth of PR8 virus was interfered with in both cortisone and control eggs. Similarly, cortisone did not abolish the autointerference observed when inactive Lee virus was followed by active Lee virus. Incubation of inactivated virus with cortisone does not reactivate it, if the cortisone is removed before inoculation into eggs. It is suggested that cortisone affects the host's cells in such a way that virus which is inactive ordinarily is able to reproduce. The effect depends on a relatively large inoculum of virus (multiplicity reactivation). K.

Correlations Between Plasma Protein Fractions, Antibody Titers, and the Passive Transfer of Delayed and Immediate Cutaneous Reactivity to Tuberculin PPD and Tuberculopolysaccharides. Cole, L. R., and Favour, C. B.: J. Exper. Med. **101**: 391, 1955.

Guinea pigs were immunized with heat-killed tubercle bacilli suspended in mineral oil. They were bled within 48 hours after a marked cutaneous reaction to PPD was obtained and their sera were pooled. Fractionation was carried out by "Method X" (Cohn) with a few variations which are described in detail. These fractions were injected intraperitoneally into normal animals which were then tested intracutaneously with PPD, Old Tuberculin, Brucellergen and other control antigens, Choucroun polysaccharide, which is part of the "toxic fraction" of tubercle bacilli, and with S 4 and S 6 polysaccharides. The serum fractions were also tested for their respective titers of hemagglutinating antibodies by the Middlebrook-Dubos method and by the Boyden method which uses red cells pretreated with tannic acid. It was found that antibody to polysaccharide occurs only in serum fraction II, the gamma globulin fraction, and that this fraction transfers anaphylactic sensitivity as well as the immediate urticarial skin reaction (maximal at 4 to 8 hours) to OT and to polysaccharides. In addition, this fraction contains all the hemagglutinating antibody for Middlebrook-Dubos sensitized sheep cells. Tuberculoprotein antibody was found entirely in a subfraction designated as fraction IV-10, consisting of alpha globulin with some albumin. This fraction passively transfers delayed type skin reactivity to PPD (maximal at 18 to 30 minutes), by 4° C. for 4 to 5 days, by freezing, and by lyophilizing. When fractions II and IV-10 are combined, there is complete inhibition of passive transfer of delayed cutaneous reactivity, but their separate in vitro hemagglutinating properties are not altered. It is suggested that an imperceptible immediate wheal type reaction may leach tuberculin from the test site and thus prevent the delayed reaction. Passive transfer studies with fraction II by the intraperitoneal and intracutaneous techniques revealed that polysaccharides produced wheal-flare reactions identical with those from OT with the difference that the polysaccharide reactions could be elicited for a longer time after transfer of sensitization. Vigorous Prausnitz-Küstner reactions were obtained consistently when fraction II was used to sensitize the skin and the site was tested with OT, S 4, S 6, or Choucroun test materials. Only two of fourteen guinea pigs tested with PPD showed immediate reactions. Adsorption of this serum with Middlebrook-Dubos-sensitized sheep red cells removed the passive transfer capacity for the immediate type reaction. Similarly, when fraction IV-10 was adsorbed with Boyden-sensitized cells its capacity to transfer delayed type reactivity was removed. K.

The Comparison of Some Tuberculins in BCG-Vaccinated and Unvaccinated Persons. Aronson, J. D., Taylor, H. C., and McGettigan, M. T.: Am. Rev. Tuberc. **70**: 71, 1954.

The relative sensitivity of different samples of Old Tuberculin (OT) and various preparations of purified tuberculins was compared by the simultaneous intracutaneous injection of paired tuberculins in unvaccinated and in BCG-vaccinated persons. A wide variation was found in the potency of different samples of OT as determied on both vaccinated and unvaccinated persons. This variation in potency was found even in different lots prepared by the same manufacturer. The differences in potency were most marked among those persons vaccinated with BCG one to four years prior to testing. The activity of OT decreased after freeze-drying. Testing of highly sensitized persons with different preparations of purified tuberculins elicited no significant differences

in potency, with the exception of PPD-S tablets. Among unvaccinated persons markedly hypersensitive to tuberculin, the incidence of positive reactions to the first dose of the different purified tuberculins was approximately the same. Among BCG-vaccinated persons tested two to five months after vaccination, comparable percentages of responses were obtained to a Danish preparation of PPD labeled RT or PT XXII, to an English preparation labeled Weybridge PPD, and to OT. When the results of testing this same group with PPD-S and with OT in similar dosage were compared, it was found that a higher percentage responded to OT. Differences in the incidence of reaction to OT and to the different preparations of purified tuberculins were most marked among those who had received BCG vaccine from one to four years previously. PPD-S tablets gave a significantly lower percentage of reactions in both unvaccinated and BCG-vaccinated persons than did PPD-S or OT. No difference could be found in BCG-vaccinated persons tested with PPD from *M. avium* and with OT, but a smaller percentage responded to PPD from the acid-fast *M. balnei* organism. Similarly, among the unvaccinated population, a smaller percentage responded to PPD from *M. balnei* than to OT. A smaller percentage of unvaccinated and BCG-vaccinated persons responded to the patch test than to the intracutaneous injection of OT or PPD-S. E. W.

Antituberculous Immunity Induced in Mice by Vaccination with Killed Tubercle Bacilli or With a Soluble Bacillary Extract. Weiss, D. W., and Dubos, R. J.: J. Exper. Med. **101**: 313, 1955.

Tubercle bacilli were extracted with methanol, dissolving out a fraction which was not toxic for mice but which induced immunity against infection with a challenge dose of tubercle bacilli sufficient to kill control animals (mice) in from 10 to 30 days. The degree of immunity was comparable to that attained with living attenuated organisms or with whole killed bacilli. Extraction by other solvents such as acetone, petrolic ether, or diethyl ether did not result in the recovery of a protective factor. Spleen counts of tubercle bacilli following challenge infection were lower in the mice treated with methanol fraction than in the controls, although not so low as in BCG-protected mice. Inherent toxicity of tubercle bacilli is discussed as a major obstacle in the separation of the protective fraction. K.